Monitoring After Childhood Cancer

Medical check-ups after childhood cancer should have two main goals: 1) to confirm continued remission and 2) to monitor for late effects of cancer or its therapy. Late effects testing includes checking for harmful effects of therapy on the brain, heart, lungs, thyroid gland, gonads (ovaries or testes), bone marrow, bones, and other soft tissues. The risk of late effects is related to the type of cancer therapy (surgery, radiation therapy, or chemotherapy) and the patient's age at the time of treatment. The effect of radiation on growth and development may not become noticeable for many years. On the other hand, chemotherapy is likely to result in early side effects, which are more often short-term, but may persist and cause problems as the survivor ages. The growing child is especially at risk for delayed late effects affecting growth and development, fertility (ability to have children), and learning and memory. The tables below summarize common late effects seen after surgery, radiation therapy, and chemotherapy.

Childhood cancer survivors should have regular medical check-ups including cancer screening tests. The recommended screening tests are based on age, sex, and specific cancer treatment. Because health screening in childhood cancer survivors is a new area of research, screening guidelines may not exist, or may change over time, as new information becomes available. Long-term survivors ready for discharge from pediatric oncology centers should ask their oncologist to recommend the appropriate screening tests their primary care doctors should order. Even if the survivor's medical care is now coordinated by a primary care doctor like a family practitioner or internist, staying in contact with the treating pediatric cancer center will keep the survivor informed about the progress of adults treated for childhood cancer and new findings in late effects research.

Taming Patient Anxiety about Late Effects

Learning about the risk of late effects after childhood cancer therapy is very distressing for many individuals. In some cases, survivors may decide not to have check-ups for fear of discovering new health problems. Remembering the following facts may relieve some of the anxiety: 1) serious late effects develop in only a small number of childhood cancer survivors; 2) late effects occur only in patients cured of their original cancer; 3) ongoing research has the potential to reduce or prevent late effects; and 4) learning about late effects may help survivors reduce their risks of late effects. Survivors should request a record of their cancer treatment history to share with all of their health care providers. Developing a relationship with a doctor who knows your cancer treatment history, risks of late effects, and recommended screening evaluations will improve the chances of early diagnosis and treatment, or in some cases, prevention of late effects. Reviewing health habits and changing behaviors known to increase disease risk provide survivors further opportunity to protect health as they age. Finally, survivors should stay informed about research in late effects since this is a rapidly growing area of research that should increase understanding about prevention and treatment of a variety of health problems that may occur after childhood cancer.

Table 1. Late Effects of Surgery

Type of Surgery	Late Effect
Brain surgery (craniotomy)	(Dependent on area of surgery) weakness of facial nerves, trunk, and extremities; problems with speech; problems with balance and coordination; problems with vision and hearing; seizures
Chest surgery (thoracotomy)	Chronic lung problems (rarely, and only if large amount of lung resected) Curvature of spine (scoliosis) Chronic pain
Any abdominal surgery (laparotomy)	Intestinal blockage
Removal of kidney (nephrectomy)	Usually none, remaining kidney enlarges and functions normally
Removal of spleen (splenectomy)	Increased risk of life-threatening blood infection by bacteria usually killed by spleen
Removal of liver lobe (hepatectomy)	Usually none, liver may regenerate, function remains normal
Pelvic surgery	Bowel or bladder incontinence; sexual dysfunction
Amputation and limb-sparing surgery	Scarring and reduced mobility of limb or joint; chronic pain, cosmetic deformity
Amputation	Psychological adjustment to limb loss
Limb-sparing surgery	Loosening or fracture of endoprosthesis

Table 2. Late Effects of Radiation Therapy

Organ	Late Effect
All tissues	Second (different) cancers
Bones and joints	Weakening of bones or joints; reduced or uneven bone growth leading to curvature of spine, short height, differences in limb size; cosmetic deformities; chronic pain
Muscle and soft tissues	Scarring or reduced growth leading to scoliosis, cosmetic deformities; chronic limb swelling (lymphedema)
Teeth and salivary glands	Lack of, or abnormal tooth development affecting enamel or roots; Chronic dry mouth leading to higher risk of cavities and gum disease
Brain	Problems with memory and learning Abnormalities of brain tissue including loss (atrophy) of brain tissue and calcium deposits in brain tissue
Vision	Cataracts Dry or light-sensitive eyes Inflammation and scarring of cornea (keratoconjunctivitis) Abnormal growth of blood vessels in eye (retinopathy)
Hearing	Scarring of ear drum or tiny middle ear bones affecting balance Damage to hearing nerve cells in ear or brain Ear wax build-up

Organ	Late Effect
Heart and blood vessels	Scarring of heart lining with fluid build-up (constrictive pericarditis with effusion) Heart valve problems Scarring and blockage of blood vessels feeding heart (coronary artery disease) Heart attack (myocardial infarction) Abnormal heart rhythms
Lungs	Lung scarring (fibrosis) resulting in stiffer lungs Problems with exchange of gases on lung surfaces (diffusion)
Stomach, bowel, and liver	Chronic diarrhea, malabsorption, intestinal strictures, liver damage
Kidneys and bladder	High blood pressure Reduced kidney function Scarring of bladder Reduced bladder capacity
Endocrine glands Pituitary gland	 Deficiency of hormones affecting growth, pubertal development and metabolism (growth hormone and other hormones controlling thyroid, adrenal, or gonadal function)
Thyroid gland	Under-production of thyroid hormone (hypothyroidism) Over-production of thyroid hormone (hyperthyroidism) Thyroid enlargement (goiter) Thyroid nodules
Testes and ovaries	Scarring of genital organs affecting sexual function Infertility (inability to father or conceive children) Males: reduced testosterone production, reduced or absent sperm production Females: reduced estrogen production; ovarian failure, early menopause

Table 3. Late Effects of Chemotherapy

Organ/Tissue	Predisposing Drug(s)	Late Effect
Brain	Methotrexate (high-dose)	Brain tissue changes (leukoencephalopathy) associated with motor weakness, behavior and learning problems, seizures
Nerves	Cisplatin Cisplatin Vincristine, vinblastine	Hearing loss Motor nerve weakness, sensory nerve changes with tingling, numbness of hands/extremities
Heart	Anthracyclines (Adriamycin, daunomycin) Cyclophosphamide (high-dose)	Weakening of heart muscle (cardiomyopathy) Heart failure Abnormal heart rhythms
Lungs	Bleomycin, BCNU Cyclophosphamide (high-dose)	Lung scarring and inflammation
Liver	Methotrexate, BCNU	Liver inflammation (hepatitis) Liver scarring (fibrosis, cirrhosis)
Kidney	Ifosfamide, cisplatin Cisplatin, carboplatin Methotrexate (high-dose) Nitrosureas (BCNU, CCNU)	Damage to kidney tubules with salt (magnesium, potassium) and protein wasting Reduced kidney filtration; Kidney failure (rare)
Bladder	Ifosfamide, cyclophosphamide	Bleeding and irritation of bladder lining; scarring of bladder lining; bladder cancer

Tissue/Organ	Predisposing drug(s)	Late Effect
Testes and ovaries	Alkylating agents (chlorambucil, cyclophosphamide, procarbazine, CCNU, BCNU, nitrogen mustard, chlorambucil)	Females: low estrogen levels; lack of pubertal development; inability to conceive children; early menopause; ovarian failure Males: low sperm count; inability to father children; low testosterone; low testosterone levels and lack of pubertal progress with high doses
Bone Marrow	Alkylating agents (chlorambucil, cyclophosphamide, procarbazine, CCNU, BCNU, nitrogen mustard, chlorambucil) Epipodophyllotoxins: etoposide, teniposide	Abnormal development of blood cells in the bone marrow (myelodysplasia) Acute myeloid leukemia
Bones	Corticosteroids (prednisone, Decadron), methotrexate	Weak bones (osteopenia, osteoporosis) Damage to bone joints (avascular necrosis)

Approach to a Late Effects Evaluation

The approach to a late effects evaluation should begin with a thorough physical examination followed by screening laboratory and diagnostic imaging determined by the individual patient's risks of treatment sequelae. The following specific systematic evaluations should be considered based on the survivor's chemotherapy and radiotherapy exposures and clinical symptoms.

1) Musculoskeletal/Skin
   a. Height, weight, and crown-rump measurements
   b. Complete growth grid during and after therapy
   c. Notation of abnormal musculoskeletal findings related to radiotherapy (include hypoplasia of bone/muscle, scars, scoliosis, etc.)
   d. Photographs of irradiated areas to document skin and musculoskeletal changes.
   e. Assessment of adaptation to amputation

2) Dental
   a. Notation of chemotherapy and/or radiotherapy induced structural changes like poor enamel/root formation and xerostomia.
   b. Assessment of dental hygiene and education about its importance in preventing caries and periodontal disease.

3) Endocrine
   A. Thyroid
      1. Careful exam of thyroid for hyperplasia and nodules
      2. Thyroid function studies in patients given cervical irradiation
      3. Screening thyroid ultrasound if exam is suspicious

   B. Gonadal
      1. Tanner stage of breasts pubic/axillary hair, and genitalia
      2. Testicular size (length x width) or volume (using Prader orchidometer)
      3. Fertility history-regularity of menstrual periods, symptoms of sexual dysfunction, attempts at pregnancy.
      4. Consider FSH and LH in patients who received alkylating agent chemotherapy and/or radiotherapy below the diaphragm
      5. Semen analysis

   C. Pituitary
      1. Assess growth deceleration caused by radiation- or chemotherapy induced growth hormone deficiency.
      2. Screen, if clinically indicated, for other pituitary hormone deficiencies.

4) Pulmonary
   a. Pulmonary function studies in patients who received bleomycin and/or chest radiotherapy.
   b. Chest radiograph to document radiation changes.
   c. Counsel about increased risk of lung cancer in patients who received lung irradiation and who smoke.

5) Cardiac
   a. Electrocardiogram/echocardiogram in patients given anthracyclines and/or chest radiotherapy.
   b. Rest/exercise MUGA scan in clinically symptomatic patients
   c. Holter monitoring in patients with history of syncope or suggestive of paroxysmal arrhythmias.

6) Genitourinary
   a. Note blood pressure
   b. Screening urinalysis for hematuria and proteinuria in patients given cyclophosphamide, ifosfamide, and/or bladder irradiation
   c. Renal function studies in nephrectomized patients and those given cisplatin, carboplatin, and/or renal irradiation.

7) Gastrointestinal
   a. Elicit history for late sequelae such as malabsorption, adhesive/obstructive complications.
   b. Screen hepatic function if clinically indicated by treatment history.

8) Vision and Hearing
   a. Evaluation for cataracts, optic atrophy, and retinopathy in irradiated patients.
   b. Screening for high frequency hearing loss in patients given cisplatin chemotherapy and other renal toxic drugs like aminoglycosides

9) Infectious
   a. Screen for Hepatitis B, C, and HIV if high risk by number of transfusions administered during therapy or clinically indicated otherwise.
   b. Document frequency of infections that could be related to prolonged immunosuppression.
   c. Review fever precautions in splenectomized patients and assure immunization with Pneumovax, Hemophilus influenza B, and meningococcal vaccines.

10) Second malignant neoplasms
   a Thorough examination of the skin and soft tissues in radiation volumes
   b. Screening complete blood count with differential and platelets in patients given alkylating agents and epipodophyllotoxins
   c. Review of the risks of cancer-producing behaviors coupled with previous cancer therapy.

11) Neuropsychological
   a.. Social history to determine school/work performance and behavioral problems.
   b. Neurologic exam to document persistent neuropathy or focal deficits
   c. Referral for neuropsychological testing in patients with histories of learning or behavioral problems.
   d. Consider diagnostic neuroimaging to document structural changes related to chemotherapy and cranial irradiation

12) Genetic
   A. Retinoblastoma
      1. Heritable or nonheritable type, sporadic cases may be either
      2. Heritable type with autosomal dominant inheritance and high penetrance (80% to almost 100%)
      3. Heritable type has $\geq$ 30% risk to develop second malignancy
      4. Bilateral sporadic cases are always heritable - offspring will have 50% risk of having retinoblastoma
      5. Unilateral sporadic cases may be heritable or nonheritable - 10-12% are heritable, offspring have 5-6% risk of having retinoblastoma

   B. Wilms' Tumor
      1. 1-2.4% are familial with autosomal dominant inheritance with incomplete penetrance - all family members should be screened
      2. Theoretical risk of transmission to offspring of bilateral Wilms' tumor survivors although this has infrequently been reported - some investigators recommend screening offspring every 3 to 6 months until age 5 since bilateral disease implies a germline mutation that can be passed to offspring.

   C. Neurofibromatosis
      1. Autosomal dominant transmission (NF gene - chromosome 17) so 50% risk in offspring but with variable penetrance.
      2. Increased risk of benign and malignant tumors (primarily in bowel wall, kidney and heart); risk of CML in young
      3. Consider evaluation for malignancy if old or new neurofibroma increase in size or develop pain suddenly.

13) Psychosocial
    a. Assess patient/family adjustment problems
    b. Explore concerns about relapse
    c. Determine educational/vocational/employment problems
    d. Discuss issues related to body image
    e. Evaluate psychosocial development, i.e., social skills, peer relationships

14) Cancer Prevention/Healthy Lifestyles
    a. Review simple cancer screening tests like breast and testicular self-examination
    b. Review radiotherapy volumes and encourage observation for skin (particularly nevi) and soft tissue changes in these area(s)
    c. Review adverse health effects of tobacco use and excessive sun exposure
    d. Discuss routine teen health issues such as responsible sexual behavior, seat belt use, alcohol/drug use, particularly when driving